UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

September 9, 2014

MEMORANDUM

Subject: **2-Butyl-1,2-Benzisothiazolin-3(2H)-One (BBIT):** Estimated Inhalation MOEs for Machinists Using BBIT Treated Metal Working Fluids

PC Code: 098951	DP Barcode: 421676
Decision No.:	Registration No.: 1258-1249 and 1258-1267
Petition No.: N/A	Regulatory Action: label amendment
Risk Assess Type: N/A	Case No.: N/A
TXR No.: N/A	CAS No.: 4299-07-4
MRID No.: N/A	40 CFR: N/A

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The registrant submitted a label amendment for the use of 2-butyl-1,2-benzisothiazolin-3(2H)-one (BBIT) in EPA Reg No. 1258-1249 and 1258-1267 and is seeking removal of "enclosed systems only" label restriction for BBIT used as a preservative in metalworking fluid (MWF). The application rate for BBIT ranges from 25 to 200 ppm. The removal of the restriction triggers additional toxicology data requirements.

The Agency has determined that the proposed label amendment request to remove the enclosed system restriction will result in inhalation exposures for machinists using BBIT-treated MWFs. The Agency requested that the registrant submit a route-specific 90-day inhalation toxicity for BBIT to support the risk assessment (D413879). The registrant responded with an argument and justification of bridging to existing data on 4,5-dichloro-2-n-octyl-4-isothiazolin-3-one (DCOIT), 5-chloro-2-methyl-4-isothiazolin-3-one and 2-methyl-4-isothiazolin-3-one (CMIT/MIT), and 2-N-octyl-4-isothiazolin-3-one, octylthinone (OIT) in lieu of submitting the 90-day inhalation study for BBIT (MRID 49399001).

In response to the registrant's submission, this memo includes the Agency's preliminary Margins of Exposure (MOEs) using Human Equivalent Concentrations (HECs), based on the registrant's proposal of using inhalation toxicity data for DCOIT, CMIT/MIT and OIT, to estimate the inhalation risk for machinists exposed to BBIT-treated MWF. The preliminary MOEs, some of

which are less than the target MOE of 30, suggest that the registrant needs to provide a data bridging rationales on which chemical(s) would be the most appropriate surrogate(s) to assess the potential inhalation risk for BBIT (also may consider Benchmark Dose [BMD] approach). Otherwise, an inhalation toxicity study on BBIT itself may be warranted to evaluate the inhalation risk related to exposure to BBIT. This memo, however, does not necessarily represent the Agency's conclusion and/or position of data bridging for isothiazolone biocide group as a whole.

I. Existing Subchronic Inhalation Toxicity Data

1. 4,5-dichloro-2-n-octyl-4-isothiazolin-3-one (DCOIT):

CITATION: Hagan, J.V. and Wanner, F.J. (1994): Antifoulant C9211 HQ (RH-287): Thirteen Week Nose-Only Inhalation Toxicity Study in Rats. Toxicology Department, Rohm and Haas Company. Report No. 89R-256, July 26, 1994. MRID 43487501. Unpublished.

EXECUTIVE SUMMARY: In a subchronic inhalation toxicity study (MRID 43487501) groups of 32 male and 32 female Crl;CD BR rats/dose received nose-only inhalation exposure for 6 hours per day, 5 days per week, for thirteen weeks to either air, an aerosol of o-xylene (the vehicle) at 238.5 mg/m^3, or RH-287 (32.6% a.i. in xylene) at concentrations of 0.02, 0.63, and 6.72 mg/m^3. At the end of the thirteen week exposure period, half of the animals in each group were necropsied, 5 from each group were necropsied at six months, and the remaining animals were necropsied at the end of a one-year recovery period. Mean mass median aerodynamic diameter of RH-287 was 1.4 μm, and the mean geometric standard deviation was 4.6, with 72% respirable fraction. Increased mortality was observed in the vehicle control group of female rats during the exposure period, but was attributed to over-restraint in the nose-only tubes. There was no other treatment-related increase in mortality either during the treatment period or during the recovery period. The incidence of rales was increased in high dose males and females beginning at weeks 2-3 of exposure. Significant differences were observed in body weight gain between the air control and vehicle control group during treatment, indicating an effect of vehicle on body weight gain. When compared with the vehicle control, the test material resulted in decreased body weight gain of 15- 20% for male rats and 28% for female rats at the high dose level, beginning at week 2 and persisting throughout the thirteen week exposure period. During recovery, a significant rebound in body weight gain was observed for male and female rats at the high dose, suggesting an effect on food consumption; however, food consumption data were not provided in the report. No statistically significant differences were observed in treated rats vs. vehicle or control rats in clinical chemistry or hematology parameters at any dose tested, although effects on both have been observed in oral studies at doses of 100 mg/kg/day and above. Treatment-related microscopic lesions in the nose, larynx, and lungs were observed in mid- and high-dose treated rats. Minimal or mild subacute inflammation of the nose was observed in increased incidence, as was transitional respiratory epithelial hyperplasia and goblet cell hyperplasia. In the epiglottis, hyperplasia of the squamous and cuboidal epithelium was observed in mid- and high dose rats, as was chronic-active inflammation of the epiglottis. Goblet cell hyperplasia and acute inflammation was observed in increased incidence in the lungs of high dose rats. **Based upon the histopathological alterations**

observed in the nose, larynx, and lungs, the systemic LOAEC is determined to be 0.63 mg/m^3, and the systemic NOAEC is determined to be 0.02 mg/m^3.

This study is acceptable and satisfies the guideline requirement for a subchronic inhalation toxicity study (§870.3465) in the rat.

NOTE: There is a typo in the table on page 10 of the registrant's submission (MRID 49399001). The NOAEC for DCOIT should be **0.02 mg/m^3** (instead of 0.21 mg/m^3).

2. 5-Chloro-2-methyl-4-isothiazolin-3-one and 2-methyl-4-isothiazolin-3-one (CMIT/MIT):

CITATION: Hagan, J. and Baldwin, R. (1984) Kathon 886 MMPA Process: 13-Week Inhalation Toxicity Study in Rats. Toxicology Department, Rohm and Haas Company. Report No. 82R-245. MRID 148418. Unpublished.

EXECUTIVE SUMMARY: Under the conditions of the study, exposure of Crl:CD(SD)BR rats (16 rats/sex/group) to Kathon 886 (11% CMIT/3% MIT and 16.5% $Mg(NO_3)_2$ in an aqueous solution) at dose levels of 0.34, 1.15, and 2.64 mg a.i./m^3 via inhalation for 90 days resulted in a decreased body weight in the high-dose males (≈90% of control) and decreased body-weight gains in both sexes (♂/♀:≈84%/89%) at the high-dose level. There were no treatment-related deaths, and no effects were observed in the hematology, clinical chemistry, ophthalmoscopic, and gross pathology parameters monitored that could be attributed to treatment. Treatment-related lesions in the nasal turbinate were observed at the mid- and high-dose levels, which consisted of eosinophilic droplets in the anterior respiratory mucosa (2.64 mg a.i./m^3) and rhinitis in the lining of the anterior portion of the nasal cavity (1.15 and 2.64 mg a.i./m^3). These are consistent with a normal physiological response to a respiratory irritant. **The NOAEC can be set at 0.34 mg a.i./m^3, the LOAEC at 1.15 mg a.i./m^3, based on microscopic lesions in the nasal turbinates (rhinitis).** This study is classified Core Minimum, and it satisfies the guideline requirements (82-4) for a 90-day inhalation study in rodents.

3. 2-N-octyl-4-isothiazolin-3-one, octylthinone (OIT):

CITATION: Hagan, J., B. Kulwich, and J. Fisher (1989) Skane® M-8 HQ microbicide thirteen-week inhalation toxicity study in rats. Toxicology Department, Rohm and Haas. Report No. 87R-013, June 29, 1989. MRID 41544701. Unpublished.

EXECUTIVE SUMMARY: In a subchronic aerosol inhalation (nose-only) toxicity study (MRID 41544701), eleven Crl:CD®BR rats/sex/exposure group were exposed by inhalation (6 hours/day, 5 days/week) for 13 weeks to aerosolized Skane® M-8 HQ Microbicide (octhilinone, a.i. 42%, Lot No. SW 85-0311) at exposure concentrations of 0 (air), 0 (propylene glycol [PG], 123 mg/m^3), 0.05, 0.64, and 6.39 mg of octhilinone/m^3. An additional eleven rats/sex/exposure group were assigned to a fourteen-week recovery period.

The mean mass median diameter and geometric mean were 2.5 μm and 9.2, respectively, for the propylene glycol exposure group and were 1.4 μm and 5.5, respectively, for all exposure groups of octhilinone. Three deaths occurred during the study but were not considered related to the exposures. No clinical signs were observed in the 0, 0 (PG), 0.05, and 0.64 mg/m^3 groups. Clinical signs in the 6.39 mg/m^3 exposure group included: rales (males and females: 5-22/22: weeks 1-13); dyspnea (females: 3/22: week 4; 3-9/22: weeks 7-10); thriftless (males: 3/22: weeks 8 and 10) and (females: 9-22/22: weeks 7-10); and red staining of the dropping sheet (males: 11/22: week 2) and (females: 6/22: week 8). There were statistically significant decreases ($p<0.05$) in body weights (3.3 to 8.8% for weeks 1, 7, and 13) and body weight gains (11.3 to 68.9% for weeks 1, 7, and 13) in male and female rats in the 6.39 mg/m^3 group. No clinical chemistry and organ weight changes and deaths were related to the exposures. There were no gross pathological findings in exposed males or females. Histopathological findings in the male and/or females from the 6.39 mg/m^3 group consisted of secretory cell hyperplasia, squamous metaplasia, inflammation, and eosinophilic droplets in the nasal cavity at the 13-week sacrifice. During the recovery period, rales were present in the males and females from the 6.39 mg/m^3 group.

Based upon the clinical signs, the decreased body weights, fluid in the uterus, and the pulmonary histopathological findings at the terminal sacrifice for males and females in the 6.39 mg/m^3 group, the **LOAEC for 13-week inhalation exposure to octhilinone is 6.39 mg/m^3. The NOAEC is 0.64 mg/m^3.**

The study is classified as Acceptable/Guideline, satisfying the requirements for a subchronic inhalation toxicity study in rats (82-4).

II. Calculation of Human Equivalent Concentration (HEC)

(1) Determine the Point of Departure (PoD): A non-observed-adverse-effect-concentration (NOAEC) established from a subchronic inhalation toxicity study is utilized to determine the PoD. The NOAECs (all are corrected to a.i.) for the three existing inhalation toxicity studies are 0.02 mg/m^3, 0.34 mg/m^3, and 0.64 mg/m^3 for DCOIT, CMIT/MIT, and OIT, respectively, based on the histopathological changes in the nasal cavity and larynx at a next higher concentration.

(2) Adjustment of the inhalation study animal NOAECs for potential human exposures: For occupational exposure to BBIT (8 hours/day and 5 days/week), an adjustment was made as follows to account for the fact that the animals were exposed six hours per day:

$NOAEC_{8\ Hour}$ = NOAEC x (6 hours/day animal exposure ÷ 8 hours/day human exposure) x (5 days/week animal exposure ÷ 5days/week human exposure)

(3) Calculation of Human Equivalent Concentration (HEC): The 8-hour NOAEC is used to calculate a HEC as below:

$$HEC_{8\ Hour} = NOAEC_{8\ Hour} \times RDDR$$

The Regional Deposited Dose Ratio (RDDR) was calculated using the RDDR Software Program that was developed as described in Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (US EPA, 1994). Study specific inputs for this program include the mass median aerodynamic diameter (MMAD), the geometric standard deviation (GSD), and the average body weight of the test animals. Because the NOAECs were based on effects that were observed in the extrathoracic (ET) region of the respiratory system, the RDDR for the ET region was used to calculate the HEC.

The standard Uncertainty Factor (UF) of 10x for inter-species extrapolation was reduced to 3x by using HEC, resulting in a total UF of 30x (10x for intra-species extrapolation and 3x for inter-species extrapolation).

A summary is provided in the table below for calculated HECs for BBIT, based on the available inhalation toxicity data of DCOIT, CMIT/MIT, and OIT.

Table 1. HEC Calculations for DCOIT, MIT/CMIT, and OIT

Test Substance	DCOIT	MIT/CMIT	OIT
MRID	43487501	00148418	41544701
Test Animal	Crl:CD®BR rats	Crl:CD(SD)BR rats	Crl:CD®BR rats
Average Body Weight at Week 13	420 grams (Both Sexes)	400 grams (Both Sexes)	370 grams (Both Sexes)
Purity	32.6% in xylene	11%/3%	42% in propylene glycol
MMAD and GSD	1.4 µm and 4.6	1.1 – 1.4 µm and 1.9 – 2.0	1.4 µm and 5.5
Concentrations (corrected to a.i.)	0 (air control), 0.02, 0.63, and 6.72 mg/m^3, and 238.5 mg/m^3 (vehicle control)	0, 0.34, 1.15, and 2.64 mg/m^3	0, 0.05, 0.64, and 6.39 mg/m^3
Exposure Regime	6 hours/day, 5 days/week	6 hours/day, 5 days/week	6 hours/day, 5 days/week
LOAEC	**0.63 mg/m^3** based on the histopathological alterations observed in the nose (min./mild subacute inflammation and transitional respiratory epithelial and goblet cell hyperplasia), larynx (chronic-active inflammation and hyperplasia of the squamous and cuboidal epithelium), and lungs (acute inflammation and goblet cell hyperplasia at high-dose).	**1.15 mg/m^3** based on treatment-related microscopic lesions in the nasal turbinates (rhinitis).	**6.39 mg/m^3** based on the clinical signs, lower body wt and body wt gain, and micro-scopic lesion in the nasal cavity (13-wk treatment period) and microscopic lesion of squamous meta-plasia and the associated inflammatory response in the nasal cavity (14-wk recovery period).
NOAEC	**0.02 mg/m^3**	**0.34 mg/m^3**	**0.64 mg/m^3**
NOAEC$_{8\ Hour}$	**0.015 mg/m^3**	**0.255 mg/m^3**	**0.48 mg/m^3**
RDDR$_{extrathoracic\ (ET)}$	0.30	0.446	0.25
HEC	**0.0045 mg/m^3**	**0.11 mg/m^3**	**0.12 mg/m^3**
LOC for the UF (i.e. Target MOE)	30	30	30

NOAEC$_{8\ Hour}$ = NOAEC x (6 hours/day animal exposure ÷ 8 hours/day human exposure) x (5 days/week animal exposure ÷ 5 days/week human exposure)
HEC = NOAEC$_{8\ Hour}$ x RDDR

III. Calculation of Inhalation Exposure and Risk

Exposure Calculations and Assumption

The inhalation exposure of machinists to MWFs treated with BBIT were assessed by multiplying an estimated MWF aerosol concentration times the amount of BBIT that is added to the MWF. The following assumptions were used in this assessment:

- The application rates are from BBIT product labels (1258-1249 and 1258-1286).
- The maximum initial dose for noticeably fouled systems is 200 ppm. The minimum initial dose is 25 ppm.
- The maximum subsequent dose for maintenance of clean systems is 30 ppm. The minimum subsequent dose is 5 ppm.
- The maximum MWF aerosol concentration of 5.0 mg/m^3 is based on the OSHA Permissible Exposure Limit (PEL) for Oil Mists. This PEL is measured as an eight hour time weighted average (8 hr TWA).
- The average MWF aerosol concentration is 1.0 mg/m^3 based on 544 OSHA personal breathing zone (PBZ) air samples that were collected on workers at metal working facilities for the period 2000 to 2009. This value is based on the arithmetic mean of 0.8 mg/m^3 for the OSHA samples and is corrected by a factor of 20 percent to account for oil mist volatilization losses of 10 of 30 percent have been observed in literature studies during chamber testing of new and used straight oils, respectively (McAneny et al, 1995 and Park et al, 2003). The OSHA PBZ samples were collected by OSHA compliance officers in an observational manner under the authority of 29 CFR 1910.1000 to determine if workplace exposures were in compliance with the OSHA PEL. In cases where the sampling time was less than 8 hours, the 8 hour TWA was calculated by assuming that the measured aerosol air concentration represented a full eight hour day.

Risk Calculations

The risks were calculated as Margin of Exposures (MOEs) which is ratio of the HEC over the BBIT air concentration. The MOEs are listed in Table 2 and range from 4.5 to 4000 depending upon the exposure assumptions used, the surrogate chemical and the application rate. Two of the MOEs are of concern because they are less than the level of concern of 30 for the uncertainty factor. Both of these MOEs are for DCOIT, which has a lower HEC than MIT/CMIT or OIT.

Table 2 –Inhalation MOEs for Machinists Using BBIT Treated MWF in Open Systems

BBIT Application Rate[A] (ppm)	MWF Air Concentration (mg/m^3)	BBIT Air Concentration[F] (mg/m^3)	Surrogate Chemical	HEC (mg/m^3)	MOE[G]
200[B] (Max initial dose)	5.0[D]	0.0010	DCOIT	0.0045	**4.5**
			CMIT/MIT	0.11	110
			OIT	0.12	120
	1.0[E]	0.00020	DCOIT	0.0045	**23**
			CMIT/MIT	0.11	550
			OIT	0.12	600
30[C] (Max sub. dose)	5.0[D]	0.00015	DCOIT	0.0045	30
			CMIT/MIT	0.11	730
			OIT	0.12	800
	1.0[E]	0.000030	DCOIT	0.0045	150
			CMIT/MIT	0.11	3700
			OIT	0.12	4000

***MOEs in bold do not exceed the target MOE of 30.**

A. Application rates are from BBIT product labels (1258-1249 and 1258-1286)
B. Maximum initial dose for noticeably fouled systems.
C. Maximum subsequent dose for maintenance of clean systems.
D. OSHA PEL for Oil Mists measured as an eight hour time weighted average (TWA).
E. Average oil mist air concentration (n=544 samples) measured by OSHA for the period 2000 to 2009 corrected for 20 percent volatilization loss.
F. BBIT Air Concentration = BBIT Application Rate * MWF Air Concentration.
G. MOE = HEC/BBIT Air Concentration. The target MOE is 30.

IV. Risk Characterization

The risks are the greatest when comparing the estimated exposures to the HEC derived from the NOAEC of 0.02 mg/m^3 from DCOIT inhalation toxicity study. This low NOAEC may be due to an artifact in dose selection it is thirty times less than the next highest dose of 0.63 mg/m^3, which is the LOAEC. This LOAEC is within ten times the LOAEC of 1.15 mg/m^3 for MIT/CMIT and the LOAEC of 6.39 mg/m^3 for OIT.

The oil mist air sampling data collected by OSHA was collected and analyzed using a gravimetric method. This method does not distinguish between oil mists and other machine shop aerosols such as metal dusts. Although these samples could have been further analyzed using solvent extraction to separate the oil from other the particles, this extraction was not done because the samples did not exceed the OSHA-PEL and the refinement was not needed.

In addition, the OSHA sampling database does not list what type of MWF was in use during the sampling. This is important because only one type of MWF (straight oil) is oil based while the other types are water based. Because the water component of the mist would evaporate from the air sample filters, the results of air sampling where water based MWFs were in use would

represent only the non-volatile components of the MWF. Since the biocide treatment levels of MWF are based on the MWF mixture after it is mixed with water, the biocide levels in the MWF aerosols would increase as water portion evaporates. This concern is tempered; however, by literature data (Piacitelli, 2001) that indicated that the geometric mean (GM) air concentration of 359 air samples, measured gravimetrically in small shops where straight oil was being used, was 0.52 mg/m^3 which is similar to the GM of 0.50 mg/m^3 for the 544 samples collected by OSHA. Although the arithmetic mean was not reported in Piacitelli, 2001, a geometric standard deviation (GSD) of 2.09 was reported which is less than the GSD of 2.62 of the OSHA samples.

References

McAneny, 1995 Volatilization of Mineral Oil Mist Collected on Sampling Filters, McAneny, J., Leith, D. and Boundy, M., Applied Occupational and Environmental Hygiene, Volume 10, Issue 9, September, 1995.

Park, 2003. Loss of Straight Metalworking Fluid Samples from Evaporation during Sampling and Desiccation. Park, D., Kim, S., Yoon, C., American Industrial Hygiene Association Journal, Volume 64, November/December 2003, pp 837-841.

Piacitelli, 2001. Metalworking Fluid Exposures in Small Machine Shops: An Overview, Piacitelli et al, American Industrial Hygiene Association Journal, Volume 62, pp 356-370 (MRID 485605-04)*

US EPA, 1994 Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry, EPA/600/8-90/066F, Office of Research and Development, October 1994

*MRID 485605-04 has been determined by the OPP ethics reviewers to be observational in nature and did not involve intentional exposure to human subjects.